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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/532,746

09/09/2005

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C1037.70035US01

2683

23628 7590 01/29/2009
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EXAMINER

LE, EMILY M

ART UNIT

PAPER NUMBER

1648

MAIL DATE

DELIVERY MODE

01/29/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/532,746	Applicant(s) AHLUWALIA ET AL.	
	Examiner EMILY M. LE	Art Unit 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 November 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-17, 64, 65, 67 and 72-75 is/are pending in the application.
- 4a) Of the above claim(s) 6, 7, 15-17 and 67 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5, 8-14, 64-65 and 72-75 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>11/05/2008</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

1. Amended claims 15-17 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The originally claimed invention and the invention claimed by claims 15-17 are related processes. The related inventions are distinct if: (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have materially different design. The material design for the originally claimed invention an HCV infected subject that was not successfully treated using a previous non-CpG therapy, whereas, the material design of the invention encompassed by claims 15-17 is directed to a different treatment population. The treatment population for the invention encompassed by claims 15-17 is subjects that are likely to be non-responsive to a non-CpG therapy. The material designs of both inventions differ from one another. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.
2. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 15-17 are withdrawn from consideration

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as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Status of Claims

3. Claims 18-63, 66 and 68-71 are cancelled. Claims 72-75 are added. Claims 1-17, 64-65, 67 and 72-75 are pending. Claims 6-7, 15-17 and 67 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) a being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 1-5, 8-14, 64-65 and 72-75 are under examination.

Specification

4. The objection of the disclosure for noted informalities is withdrawn in view of Applicant's submission.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. The rejection of the claims under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement and enablement requirement is withdrawn in view of Applicant's submission.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

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invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. Claims 1-5, 8-14, 64-65 and 72-75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Witherell et al.,¹ as evidenced by and in view of Hanecak et al.,² as evidenced by Kamal et al.³

The claims are directed to a process comprising the administration of a CpG immunostimulatory oligonucleotide comprising the sequence of 5'X₁X₂CGX₃X₄3', wherein X is any nucleotide and the oligonucleotide is 8-100 nucleotides long to a human subject having an HCV infection that was not successfully treated using previous non-CpG therapy. Claim 2, which depends on claim 1, specifies that the non-CpG therapy includes interferon-alpha. Claims 3-5, which depend on claim 2, specify that the non-CpG therapy includes interferon-alpha-2b, interferon-alpha-2a or consensus interferon-alpha; interferon-alpha and Ribavirin; and pegylated interferon-alpha and Ribavirin, respectively. Claim 8, which depends on claim 1, requires the oligonucleotide be a C class oligonucleotide. Claim 9, which depends on claim 1, requires the process to further comprise the step of administering interferon-alpha to the subject. Claim 10, which depends on claim 9, requires the interferon alpha be interferon-alpha-2b, interferon-alpha-2a or consensus interferon alpha. Claim 11, which depends on claim 9, requires that the interferon-alpha be administered substantially simultaneously with the oligonucleotide. Claim 12, which depends on claim 1, requires the oligonucleotide

¹ Witherell et al. ISIS-14803 ISIS Pharmaceuticals. Current Opinion in Investigational Drugs, 2001, Vol. 2, No. 11, 1523-1529.

² Hanecak et al. Antisense oligonucleotide inhibition of hepatitis C virus gene expression in transformed hepatocytes. Journal of Virology, August 1996, Vol. 70, No. 8, 5203-5212.

³ Kamal et al. Peginterferon alone or with ribavirin enhances HCV-specific CD4+ T-helper 1 responses in patients with chronic hepatitis C. Gastroenterology, October 05, 2002, Vol. 123, 1070-1083.

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to comprise a backbone modification. Claim 13, which depends on claim 12, requires the backbone modification be a phosphorothioate backbone modification. Claim 14, which depends on claim 1, requires the oligonucleotide to comprise a semi-soft backbone. Claim 64 is directed to the process of claim 1 with the addition of the administration of an antiviral agent. Claim 65 is directed to the process of claim 64 with the addition that the oligonucleotide comprises a semi-soft backbone. Claim 72, which depends on claim 8, requires that the oligonucleotide comprise a semi-soft backbone. Claims 73-75, which depend on claim 64, requires that the antiviral agent be interferon-alpha, ribavirin, and that the antiviral agent be administered substantially simultaneously with the oligonucleotide, respectively.

Witherell et al. teaches a process comprising the administration of ISIS-14803 to human subjects having an HCV infection that was not successfully treated using previous non-CpG therapy. The administration demonstrates that ISIS-14803 was effective in reducing HCV viral titer in said human subjects. Witherell et al. also discloses the use of ISIS-14803 as a single antiviral agent or in combination therapy with pegylated interferon and ribavirin in HCV infected subjects. [Clinical Development section, in particular.]

Witherell et al. also discloses while ISIS-14803 is effective in reducing HCV viral titer, it is unlikely that ISIS-14803 will be effective against HCV viruses. To overcome this limitation, Witherell et al. suggests the administration of ISIS-6095 with ISIS-14803. [Current Opinion section, in particular.] Witherell et al. notes that it is possible that the multiple inhibitory mechanisms activated by ISIS-14803 and ISIS-6095, it is possible

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that the combination of ISIS-14803 and ISIS-6095 would produce synergistic effects and delay the onset of resistance.

As evidenced by Hanecak et al., ISIS-6095 is a CpG containing oligonucleotide comprising the sequence of 5'X1X2CGX3X43', wherein X is any nucleotide and the oligonucleotide is 8-100 nucleotides long. ISIS-6095 comprises a phosphorothioate backbone modification.

In view of the suggestion made by Witherell et al., it would have been prima facie obvious for one of ordinary skill in the art to administer the CpG containing oligonucleotide known as ISIS-6095 with ISIS-14803 alone or in combination of interferon and ribavirin. One of ordinary skill in the art, at the time the invention was made, would have been motivated to do so to reduce HCV viral titer in said HCV infected subjects. One of ordinary skill in the art, at the time the invention was made would have had a reasonable expectation of success for doing so because ISIS-6095 has proven to be effective at reducing HCV viral titer.

It is noted that Witherell et al. does not expressly suggest simultaneous or substantially simultaneous administration ISIS-6095 in combination with the other antiviral agents, including ISIS-14803, however, at the time the invention was made, it would have been prima facie obvious for one of ordinary skill in the art to adjust the administration protocol, including simultaneous administration. One of ordinary skill in the art, at the time the invention was made would have been motivated to do so to optimize the treatment. One of ordinary skill in the art, at the time the invention was made would have had a reasonable expectation of success for doing so because the

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determination of a workable or optimal administration protocol is routinely practiced in the art.

Regarding claims 14 and 72, while ISIS-6095 is an oligonucleotide that comprises a phosphorothioate backbone, it should be noted that Hanecak et al. discloses that the backbone is a result effective variable. Hanecak et al. teaches that modification of the backbone varies the reduction in HCV viral titer and nuclease resistance. Hence, at the time the invention was made, it would have been prima facie obvious for one of ordinary skill in the art to modify the backbone of ISIS-6095, including the use semi-soft backbones. One of ordinary skill in the art, at the time the invention was made, would have been motivated to do so to vary the effectiveness of the HCV treatment and nuclease activity of the oligonucleotide. One of ordinary skill in the art, at the time the invention was made would have had a reasonable expectation of success for doing so because the use of various and modified backbones is routinely practiced in the art.

Additionally, while it is not readily apparent from the disclosure of Witherell et al. whether the combination therapy of ISIS 14803 with pegylated interferon encompasses ineteferon-alpha-2b. However, as evidenced by Kamal et al. pegylated interferon is also PEG interferon alpha-2a. [Abstract, in particular.]

Conclusion

9. No claims are allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

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§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to EMILY M. LE whose telephone number is (571)272-0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce R. Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/EMILY M LE/
Primary Examiner, Art Unit 1648

/E. M. L./